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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,991	10/23/2003	Ian J. Tickle	620-282	4740

23117 7590 07/18/2005

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EXAMINER

NASHED, NASHAAT T

ART UNIT	PAPER NUMBER
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1656

DATE MAILED: 07/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/690,991

Applicant(s)

TICKLE ET AL.

Examiner

Nashaat T. Nashed, Ph. D.

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 June 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 98-101 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 98-101 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 3/5/04, 4/13/04, 12/23/03, 10/1/04, 7/20/04, 6/28/05
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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The application has been amended as requested in the communication filed March 11, 2005. Accordingly, claims 1-97 have been canceled, and new claims 98-101 have been entered.

The disclosure is objected to because of the following informalities: at page 10, line 12, insert -----SEQ ID NO: 3-----.

Appropriate correction is required.

Claims 98 and 101 are objected to because of the following informalities: (1) claim 98 contains the unit cell dimensions "78 Å, 100 Å, 132 Å, 90°, 90°, 90°". It should be ----- a = 78 Å, b = 100 Å, c = 132 Å, $\alpha = \beta = \gamma = 90^\circ$ -----, and (2) claim 101 contains the unit cell dimensions "a = 77 Å, B = 99 Å, C = 129 Å, (+/- 5% for a, b, and c), $\beta = 90^\circ$ ". It should be "a = 77 ± 5% Å, B = 99 ± 5% Å, C = 129 ± 5% Å, $\alpha = \beta = \gamma = 90^\circ$ -----". Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 98-101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 98, 99, and 101 are directed to a crystal of P450 3A4 from human or any other mammal, fusion protein thereof and fragments of said P450 3A4 wherein said crystal is orthorhombic in space group I222 with the specific unit cell dimension cited in the claims. Claim 100 is directed to any crystal of said P450 3A4, which its diffraction pattern presumably produce a structure defined by the atomic coordinates in Table 5 +/- a root mean square deviation from C α atoms of not more than 1.5 Å. The specification, however, only provides teaching for the crystallization of SEQ ID NO: 2 under two sets of crystallization conditions which produce crystals suitable for structure determination. SEQ ID NO: 2 is a non-glycosylated protein expressed in *E. coli* and consist of a protein which residues 3-20 of the native human P450 3A4 is substituted by SEQ ID NO: 3 to enhance the expression and a His-Tag at the C-terminus. The crystals produced under the two sets of conditions are orthorhombic crystals in space group I222 having nearly the same unit cell dimension. There is no disclosure of any particular relationship between the primary structure of the P450 3A4 and the crystallization conditions. The specification also fails to describe additional representative species of these crystals P450 3A4. In fact the specification teaches away from attempting to crystallize any

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other protein other than that of SEQ ID NO: 2, see the section of "background of crystallization" starting at page 3. Given this lack of additional representative species and the teaching of the specification as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 98-101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all crystals comprising a any P450 3A4 from any mammal or modified form thereof that may include any insertion, deletion, substitution, and combination thereof mutants and fragments thereof expressed in any host cell. Factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any crystal of P450 3A4 from any biological source, mutant thereof, or modified form thereof obtain by any method and its diffraction pattern produces a structure having the atomic coordinates in Table 5 (claim 100) or an orthorhombic crystal in space group I222 having the unit cell dimension cited in claims 98 and 101. The phrase "crystal comprises SEQ ID NO: 2" in claim 99 make the claim reads on crystals of complexes comprising SEQ ID NO: 2 wherein the complex could be a small molecule or another protein, or a crystal of a protein comprising SEQ ID NO: 2. The specification provides guidance and examples in the form of an assay to crystallize the non-glycosylated polypeptide of SEQ ID NO: 2 expressed and purified from *E. coli*, see the cexamples. The specification provides an assay regarding the state of the art of crystallization; see the "Background of Crystallization" section starting at page 3, in particular, the first paragraph. The examiner in agreement with every statement made in said section, and could not have found a better characterization of the state of the art. At page 3, line 38, it states "each protein crystallizes under a unique set of conditions, which cannot be predicted in advance". While molecular biological techniques and genetic manipulation to make any protein in glycosylated or non-glycosylated form are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of specific protein and its complexes is lacking. As indicated by the applicants in the specification and is well established in the art that obtaining a protein in a crystal form is

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highly unpredictable. The skilled artisan would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization conditions, its mutants may or may not crystallize under the same conditions. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallized. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography, see the specification at page 4, line 11. Thus, searching for a crystallization conditions for a polypeptide comprising P450 3A4 having any sequence, fragment thereof, or mutants thereof glycosylated or non-glycosylated that is suitable for X-ray crystallography to obtain the specific crystals cited in claim 98 and 101 is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. It should be noted that the atomic coordinates is not the characteristic of the crystal, they characterize the three-dimensional structure of a protein/enzyme, which is an intrinsic property of the protein/enzyme. The X-ray diffraction pattern, which is not part of the record in this application, is a characteristic of the crystal, and thus, claim 100 reads on any crystal comprising P450 3A4 having any amino acid sequence. The amount of experimentation to identify crystallization conditions for any particular P450 3A4 from any biological source as well as modified form thereof and expressed in any host cell and identifies a crystal suitable for structure determination by X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization conditions for the wild-type P450 3A4 or modified form thereof which can be crystallized where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid sequences of the P450 3A4 to be crystallized, and the exact crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography and having the crystal parameters cited in claims 98 and 101. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 100 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The atomic coordinates listed in Table 5 represent the three-dimensional structure of the polypeptide of SEQ ID NO: 2, and not the crystal. The X-ray diffraction pattern, which is not part of the record in this application, is characteristic of the crystal of P450 3A4 of SEQ ID NO: 2. For examination purposes only, it is assumed that the claim means a crystal, which its diffraction pattern can be solved into a three-dimensional structure defined by the atomic coordinate listed in Table 5.

Allowable subject matter:

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Claims directed to a specific crystal of P450 3A4 of SEQ ID NO: 2 would be considered favorably. The instant claims are free of prior art of record.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on TWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Nashaat T. Nashed, Ph. D.
Primary Examiner
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